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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,794	03/17/2005	Jorge Victor Gavilondo Cowley	976-20PCT/US	6673

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EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,794	GAVILONDO COWLEY ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-36,39-42 and 47-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-36,39-42 and 47-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/7/08 has been entered.

2. Claims 32-36, 39-43 and 47-56 are all the pending claims for this application.

3. Claims 37, 38 and 44-46 were canceled and new claims 47-56 were added in the response of 7/7/08.

4. Claims 32-36, 39-42 and 47-56 are all the pending claims under examination.

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, second paragraph

5. The rejection of Claim 46 for the recitation “comprising an amino acid sequence as set forth in SEQ ID NO:16 *and* SEQ ID NO:17” is withdrawn and moot for the cancelled claim.

Rejections Maintained

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. The rejection of Claims 32-36 and 39-42 (and new Claims 47-56) under 35 U.S.C. 103(a) as being unpatentable over Tormo et al. (APMIS 97(12):1073-80 (1989); cited in the 892 form of 3/6/07; Abstract) in view of Freyre et al. (J. Biotechnol. 76:157-163 (2000); cited in the PTO 892 form of 6/7/07) as evidenced by Ayala et al. (Conf. On Plant-Made Pharmaceuticals 2005; Abstract; cited in the PTO 892 form of 6/7/07) and further in view of Hollinger et al. (PNAS 90:6444-6448 (1993); cited in the IDS of 1/24/05 and the 892 form of 3/6/07) is maintained.

New Claims 47-56 are joined under the outstanding the rejection because the generic claims are drawn to the scFv "comprising" SEQ ID NO: 16 (Claims 47) and the diabody "comprising" SEQ ID NO: 17 (Claim 52).

For purposes of review, the rejection was set forth in the Office Action of 1/4/08 as follows:

> "Claims 32-36 are interpreted as being drawn to a monomeric scFV comprising amino acid sequence of SEQ ID NO:16 which binds to human CEA (Claim 32), further comprising a detectable agent (Claim 33), further where the detectable agent is a radioactive label (Claim 34) or a reporter molecule (Claim 35); and pharmaceutical composition comprising the sequence of SEQ ID NO:16 and a carrier (Claim 36).
>
> Claims 39-42 are interpreted as being drawn to a divalent scFV comprising amino acid sequence of SEQ ID NO:17 which binds to human CEA (Claim 39), further comprising a detectable agent (Claim 40), further where the detectable agent is a radioactive label (Claim 41) or a reporter molecule (Claim 42); and pharmaceutical composition comprising the sequence of SEQ ID NO:16 and a carrier (Claim 43).
>
> *[section relating to cancelled Claim 46 is deleted]*

The instant claimed monomeric scFv of SEQ ID NO:16 and the divalent scfv or diabody of SEQ ID NO:17 and pharmaceutical compositions comprising the same, were prima facie obvious at the time of the invention in view of Tormo, Freyre and Hollinger as evidenced by Ayala.

Tormo discloses the hybridoma CB/ior-CEA.1 which produces the murine Mab as being highly specific for human CEA with no cross-reaction with CEA-related molecules that shows no recognition of normal tissues, except for cells of the normal colon epithelium with polarized CEA expression. Applicants specification specifically teaches that the VH and VL domains comprising the scFv of SEQ ID NO:16 and 17 were derived from the antibody produced by the CB/ior-CEA.1 hybridoma of Tormo (see Example 1, p. 10, lines 35-39: "Total RNA from 10^6 cells of the mouse hybridoma CB/ior-CEA.1 (Tormo B. et al. APIMS. 97:1073-1080, 1989) was extracted with the TriPure^{TM} reagent…".) ("The discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property, which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1997). Tormo does not disclose Ab constructs such a monomeric and diabody scFvs using the VH and VL domains from the parent antibody. Freyre as evidenced by Ayala and Hollinger rectifies this deficiency in its disclosure.

The scFv produced by Freyre et al. in 2000 using the VH and VL of CB/ior-CEA.1 was producible at high levels but reduced in affinity because numerous changes had been introduced into the VH/VL domains during PCR cloning as evidenced by Ayala. Ayala specifically teaches "A new scFv was constructed from newly amplified CB/ior-CEA.1 VH and VL genes, taking care to avoid the potential introduction of PCR mutations." And as evidenced by Ayala, Hollinger provided an alternative means for producing multivalent scFv forms and maintaining the integrity of the original VH and VL domain sequences of the parent antibody.

Hollinger discloses recombinant antibody fragments using variable domains encoded by genes from mouse hybridomas to make constructs for expressing scFv, bivalent and bispecific antibody fragments that have the advantages of retaining the antigen recognition of the parent antibody, being small in size, assembled in vivo and harvested directly from culture supernatant.

One skilled in the art would have been motivated to have combined the techniques of Tormo, Freyre and Hollinger as evidenced by Ayala to obtain an improved antibody fragment having the binding properties of the parent CB/ior-CEA.1 antibody and the advantages of being readily producible as a properly assembled and secreted antibody fragment by transfected cells in vitro or in vivo, and been reasonably assured of success in producing such based on the disclosures of Tomoro, Freyre as evidenced by Ayala and Hollinger. The Tormo CEA antibody was highly selective and non-crossreactive for purposes of using such an antibody in targeted diagnostics or therapeutics for CEA-expressing tumors, and because obtaining smaller sized Ab fragments was more desirable for retaining antigen binding and for tumor penetration, one skilled in the art would have been motivated to have obtained scFv from the CB/ior-CEA.1 parent antibody based on Freyre, and because Freyre's scFv was already established at the time of the invention to retain antigen specificity albeit reduced affinity compared with the parent Ab as evidenced by Ayala, one would have been further motivated to have obtained an scFv or diabody which possessed reproducible and approximate binding properties to the parent Mab based on the disclosure of Hollinger for producing scFvs replicating the binding properties of the respective parent antibody. Taken together, one skilled in the art would have been reasonably assured of success in producing the instant claimed CEA antibody embodiments based on the disclosures of Tormo, Freyre as evidenced by Ayala and Hollinger because all the materials and reagents were available for producing the recombinant CEA Abs, and as evidenced by Freyre the importance of VH and VL sequence fidelity in generating a scFv with high affinity binding was established and Hollinger provided an alternative method to for cloning VH and VL domains from a parent Mab into a scFv or diabody structure in order to produce a smaller sized but high affinity antibody variant of the parental Mab. Further all of the reference appreciated obtaining small sized fragments for pharmaceutical applications.

Thus for the reasons above, the claims were prima facie obvious at the time of the invention over Tormo, Freyer as evidenced by Ayala and Hollinger."

Applicants' allegations on pp. 6-12 of the Response of 7/7/08 have been considered but are not found persuasive.

-) Initially, Applicants allege on p. 6 "all of the claim limitations must be taught or suggested by the prior art."

Response to Arguments

Under the recent KSR decision, the cited references of art are not required to "*explicitly* teach or suggest" all of the steps or elements. The Supreme Court has determined in *KSR International Co. v. Teleflex, Inc.*, 550 U.S._, 82, USPQ2d 1385 (2007), that "a person of ordinary skill attempting to solve a problem will" not " be led only to those elements of prior art designed to solve the same problem……" (KSR, 550 U.S. at_, 82 USPQ2d at 1397). In addition, the court found that "When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variant, 35 USC 103 likely bars its patentability" (KSR, 550 U.S. at_, 82 USPQ2d at 1396). Further the court found that the Federal Circuit has erred in applying the teaching-suggestion-motivation test in an overly rigid and formalistic way, in particular by concluding "that a patent claim cannot be proved obvious merely by showing that the combination of elements was 'obvious to try'" (KSR, 550 U.S. at_, 82 USPQ2d at 1397) and has further determined that "…….[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results" (KSR, 550 U.S. at_, 82 USPQ2d at 1395). The court further found that "…… the conclusion that when a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the

combination is obvious" (KSR, 550 U.S. at_, 82 USPQ2d at 1395-1396). Thus, when considering obviousness of a combination of known elements, the operative question is "whether the improvement is more than the predictable use of prior art elements according to their established functions" ((KSR, 550 U.S. at_, 82 USPQ2d at 1396).

-) Next, Applicants allege "scFv antibody fragments developed by previous investigators (e.g., by Freyre, 2000, and Ayala, 1992) failed to exhibit a high affinity for the target antigen CEA and a proper biodistribution in test animals. See the specification at page 2, lines 29-40; see also Ayala (2005), first paragraph, which states that the affinity of the scFv disclosed in Freyre "was shown to be 200 times lower than that of the Fab obtained by enzyme digestion of the original Mab (Perez L et al., 1996)."). Accordingly, merely having "all the materials and reagents" available for producing the recombinant CEA Abs is not sufficient for a reasonable expectation of success for arriving at the claimed scFv fragments".

Response to Arguments

Freye as evidenced by Ayala established that the VH and VL domains from Tomoro's CB/ior-CEA.1 antibody could be cloned, used in the construction of a scFv construct and measured for its binding affinity against the parent antibody VH/VL domains found in a Fab fragment. Thus, the materials, reagents and techniques for generating the scFv constructs were all available at the time of the invention. All of these techniques and reagents are what allowed the artisan to determine that a loss of binding affinity resulted from PCR cloning error in the VH/VL domains of Freye compared to Tomoro's parent antibody.

-) Next, Applicants allege “Contrary to the examiner's assertion, however, "the importance of VH and VL sequence fidelity in generating a scFv with high affinity binding" was not established at the time of the invention in 2002. At the time of the invention, there was nothing predictable about how or what to modify from the CB/ior-CEA. 1 hybridoma of Tomoro or the the scFv antibody fragments of Freyre in order to arrive at the claimed scFv antibody fragments.”

Response to Arguments

The ordinary artisan in viewing the reference disclosures of Tomoro and Freye as evidenced by Ayala would have found more than sufficient motivation to avoid introducing PCR mutations into the VH and VL domains of Tomoro's CB/ior-CEA.1 antibody in order to avoid the significantly decreased binding affinity. Thus, cloning VH and VL domains having exact identity to the VH and VL domains of Tomoro’s parent antibody to maintain the binding affinity of the scFv would have been obvious in view of Freye and Ayala teaching that cloning error produced undesirable binding properties.

-) Next, Applicants allege citing Ayala is impermissible hindsight because Ayala is published 3 years after the priority date.

Response to Arguments

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does

not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Freye taught that the binding affinity was significantly reduced compared to Tomoro's parent antibody, and achieving a scFv with a similar if not identical binding affinity would have been obvious if not a source for the motivation to generate a construct having the VH and VL domains with similar binding characteristics as the parent antibody.

Finally, Ayala is effective as art to show inherency for the PCR-introduced mutations in the CB/ior-CEA.1-derived VH and VL domains for the scFv construct of Freye pursuant to MPEP 2131.01:

> ""III. To show that a characteristic not disclosed in the reference is inherent"...Note that as long as there is evidence of record establishing inherency, failure of those skilled in the art to contemporaneously recognize an inherent property, function or ingredient of a prior art reference does not preclude a finding of anticipation. *Atlas Powder Co. v. IRECO, Inc.* 190 F3d 1342, 1349, 51 USPQ2d 1943, 1948 (Fed. Cir. 1999)...Also note that the critical date of extrinsic evidence showing a universal fact *need not antedate* the filing date (MPEP 2124)."

-) Applicants allege the results for the claimed scFvs are unexpected over the prior art because the claimed scFvs were compared to the scFv designated "F3" and which corresponds to the scFv of Freye (2000). Example 8 shows the binding affinity for

CEA for the scFv and diabody of the invention (SEQ ID NOS: 16 and 17, respectively) against F3 of Freye is improved. Example 9 shows the radiometric detection of CEA-expressing melanoma in vivo with radio-labeled scFv and radio-labeled diabody of the invention compared to "F3" is more highly detectable.

Response to Arguments

The examiner respectfully submits that it would have been prima facie obvious to select a scFv clone having similar if not identical VH and VL as the parent CB/ior-CEA.1- VH and VL domains with the scFv having similar if not improved binding affinity for CEA antigen compared to any antibody (scFv) having a lower affinity that was already known to exist in the art, i.e., F3. As the lower affinity was produced as a result of PCR cloning error as evidenced by Ayala, it is not unexpected that the ordinary artisan would have found motivation to re-create or regenerate the VH and VL domains from a parent CB/ior-CEA.1 antibody of Tomoro in the scFv to recapture or regain comparable binding affinity of the parent.

The rejection is maintained.

Conclusion

7. No claims are allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LAB

/David J Blanchard/
Primary Examiner, Art Unit 1643